Penbutolol in hypertension, alone and in combination with furosemide

A long-term multicentre study

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Summary

Penbutolol is a new, potent and long-acting non-cardioselective ß-adrenergic blocker which has been evaluated in a 6-month open study of patients with moderate essential or renal hypertension. Eighty-two patients entered the study and 69 completed at least 3 months of treatment. Two-thirds of these showed a good response to penbutolol given alone as a single daily dose of either 40 mg or 80 mg. The major reduction in blood pressure occurred within the first 2 weeks of active therapy. This response was maintained for the entire study period. Blood pressure reduction after penbutolol did not correlate with the small reduction in heart rate observed. The remaining patients were treated with a combination of penbutolol and furosemide and most had achieved satisfactory control of their blood pressure by the end of the study.

Penbutolol was well tolerated and produced no serious adverse effects. Some patients developed gastro-intestinal side-effects at the beginning of treatment which subsequently resolved. One patient with chronic glomerulonephritis showed a marked deterioration in renal function during the study. This may well have been related to disease progression. No other significant changes in biochemical or haematological parameters were observed.

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Penbutolol (1-tertbutylamino-3-(*o*-cyclopentylphenoxy)2-propanol) is a non-cardioselective ß-adrenergic receptor blocker with partial agonist activity.[1,2] Clinically it is approximately four times as potent as propranolol, but has a longer duration of action.[3-5] Penbutolol has been shown to be an effective anti-anginal and antihypertensive agent,[6-8] and there appears to be no loss of efficacy when the drug is administered as a single daily dose.[9-12] A preliminary review of its pharmacological properties and therapeutic efficacy in hypertension and angina pectoris was published recently.[13]

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This report describes a study in which the long-term efficacy and tolerability of penbutolol alone and in combination with furosemide in patients with moderate hypertension were evaluated.

Patients and methods

The study was an open multicentre evaluation conducted by 8 investigators. Ambulatory patients of either sex, aged between 25 and 65 years, with moderate essential or renal hypertension were eligible for entry to the study.

Exclusion criteria were cardiac decompensation, valvular heart disease, chronic obstructive airways disease, diabetes mellitus, atrioventricular block, bradycardia (heart rate $\leq$ 60/min) and concomitant vasodilator or tricyclic antidepressant therapy. All patients gave informed consent to participation in the study.

The study commenced with a placebo run-in period lasting 2 or 3 weeks during which time each patient received 1 placebo capsule (matching the penbutolol capsule in size, shape and colour) each morning. Subsequently, active treatment comprised penbutolol 40 mg given once daily. Dose adjustments or the addition of furosemide were made according to patients' response to treatment after fortnightly intervals. The dosage scheme is shown in Table I.

TABLE I. SEQUENCE OF DOSE INCREMENTS

1. **Placebo once a day**
2. **Penbutolol 40 mg once a day**
3. **Penbutolol 80 mg once a day**
4. **Penbutolol 80 mg + furosemide 20 mg once a day**
5. **Penbutolol 80 mg + furosemide 40 mg once a day**
6. **Penbutolol 80 mg + furosemide 40 mg a.m. + penbutolol 40 mg p.m.**

Patients were seen at the beginning and end of the placebo run-in period, at fortnightly intervals for the first month of active treatment, and subsequently monthly for a further 5 months. At each visit blood pressure and heart rate were recorded supine (after 5-10 minutes lying down), erect (after 1-2 minutes standing), and in most of the patients after exercise (which was standardized for individual patients). A check-list of adverse effects was also completed each time.

At the beginning of active treatment blood was taken for haematological and biochemical investigation. Ophthalmological examination was carried out, as was routine urinalysis. All of these investigations were repeated at the end of the 6-month treatment period.

Results

Of the 82 patients admitted to the study 13 did not complete at least 3 months' treatment. The characteristics of the remaining

TABLE II. CHARACTERISTICS OF PATIENTS STUDIED

	Male	Female
No.	**25**	**44**
Age (yrs)		
Mean ± SD	**51,0 ± 10,2**	**46,1 ± 10,3**
< 30	**0**	**4**
30-45	**6**	**11**
46-60	**14**	**28**
> 60	**5**	**1**
Body weight (kg)		
Mean ± SD	**76,0 ± 12,7**	**66,5 ± 11,9**
Range	**59 - 100**	**43 - 97**
Essential hypertension	**22**	**41**
Renal involvement	**3**	**3**
Retinopathy		
Grade I	**16**	**28**
Grade II	**7**	**12**
Grade III/IV	**2**	**4**
Serum creatinine (mg/dl)		
Mean ± SD	**1,02 ± 0,29**	**1,01 ± 0,67**
Range	**0,5 - 2,0**	**0,6 - 4,9**
Baseline diastolic BP (mmHg) (standing)		
Mean ± SD	**110,3 ± 12,9**	**109,2 ± 13,3**
< 100	**2**	**8**
100 - 109	**4**	**10**
110 - 119	**13**	**15**
> 119	**6**	**11**

69 patients are shown in Table II. The majority of patients (63) were diagnosed as having essential hypertension, and 6 patients had hypertension associated with renal disease.

Withdrawals

Of the 13 patients who were not included in the analysis, 7 stopped coming to the clinic for reasons unknown. Six of these had been receiving penbutolol 40 mg daily for 1-2 months but there was no indication of any particular problem with it. Similarly, the 7th patient had been taking penbutolol 80 mg and again had appeared to tolerate it well.

One patient stopped the treatment (after 10 weeks on penbutolol 40 mg) because she was 'feeling better' and subsequently her blood pressure was noted to be 130/80 mmHg. Two patients were withdrawn because of lack of response on the highest dose of penbutolol (120 mg) plus furosemide (40 mg) (one after 2 months' treatment and the other after 3 months).

Three patients withdrew because of unwanted effects, 1 after only 1 week on penbutolol 40 mg because of nausea and dyspepsia. Another discontinued treatment for no apparent reason after 3 months (on 80 mg penbutolol), having experienced two anginal attacks; and the third also stopped taking the capsules (after 1 month on penbutolol 80 mg plus furosemide 20 mg) and then developed symptoms of dizziness, sweating and depression. This last patient appears to have suffered withdrawal effects on discontinuing ß-blocker therapy abruptly.

Blood pressure

To avoid excessive duplication, only the results of the supine blood pressure and pulse readings will be referred to in detail. Conclusions based on measurements with the patient supine can readily be extrapolated to the other observations made in the erect position and after exercise because excellent correlation coefficients ($P < 0{,}001$) were found for all comparisons (supine *v.* erect and supine *v.* exercise).

Alterations in blood pressure are commonly expressed as mean readings during therapy (Fig. 1). Such a method has the advantage of showing clearly the time profiles of changes resulting from therapy, but its potential disadvantage is possible concealment of interindividual variability in response to therapy. Patients receiving penbutolol alone had a lower baseline blood pressure (mean ± SD 173,3 ± 22,4/107,3 ± 11,9 mmHg) at the end of the placebo run-in period compared with patients subsequently requiring a diuretic (188,9 ± 26,3/111,4 ± 14,4 mmHg). Penbutolol alone was associated with a fall in mean blood pressure over the first 2 weeks of therapy to 148,2 ± 16,8/91,7 ± 11,0 mmHg ($P < 0{,}01$), but much less change occurred thereafter (final mean blood pressure 136,1 ± 12,7/86,7 ± 8,3 mmHg). Patients ultimately requiring a diuretic, as well as being more hypertensive at the onset, showed a much smaller reduction in blood pressure on penbutolol alone, with a mean fall, compared with placebo, of 9,1/3,0 mmHg on 40 mg of the drug and a further small drop (3,2/5,3 mmHg) when this dose was doubled. The addition of furosemide produced an additional mean fall of 11,7/9,3 mmHg. Increasing the dose of furosemide to 40 mg or that of penbutolol above 80 mg produced little additional effect. The final mean blood pressure on combined therapy was 157,3 ± 19,4/90,9 ± 10,0 mmHg at 6 months.

A picture of the pattern of response is given by the frequency histograms in Fig. 2. These data have been analysed statistically, using a 2 x k contingency χ^2 test. The clear leftward shift for both

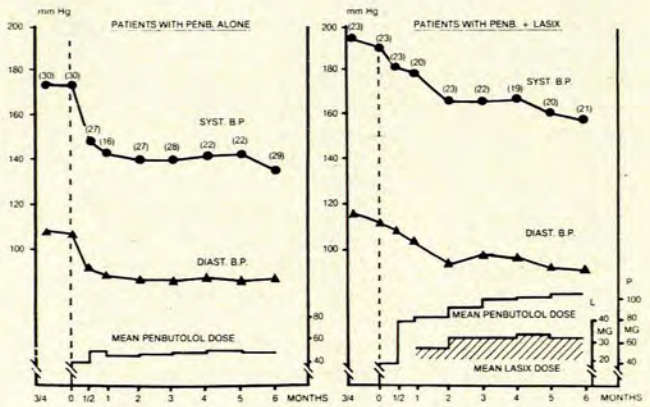

Fig. 1. Influence of addition of furosemide (Lasix) to penbutolol treatment and doses of the two drugs.

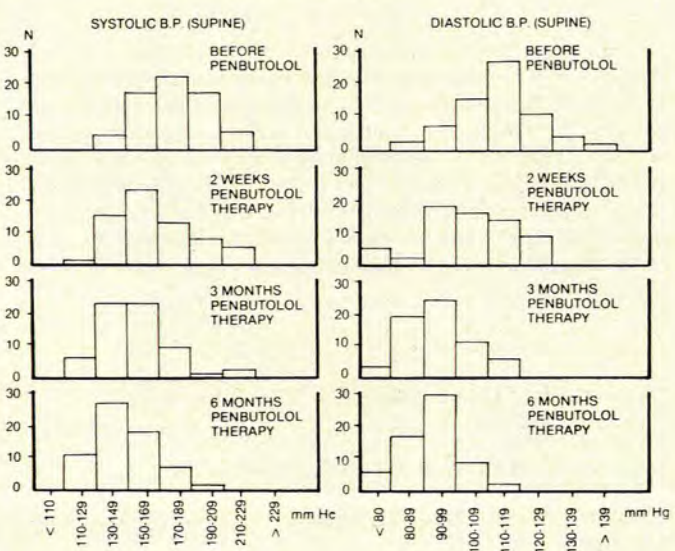

Fig. 2. Frequency histograms showing therapeutic response to penbutolol.

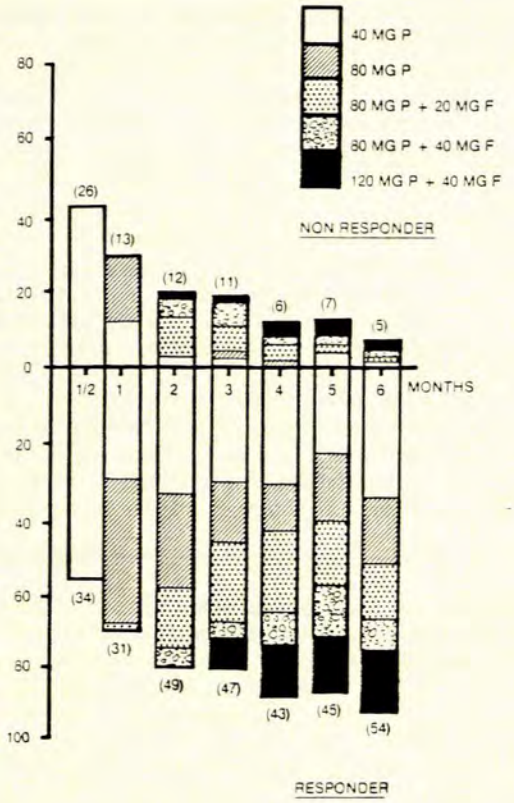

Fig. 3. Percentages of 'responders' and 'non-responders' at each visit (supine systolic blood pressure).

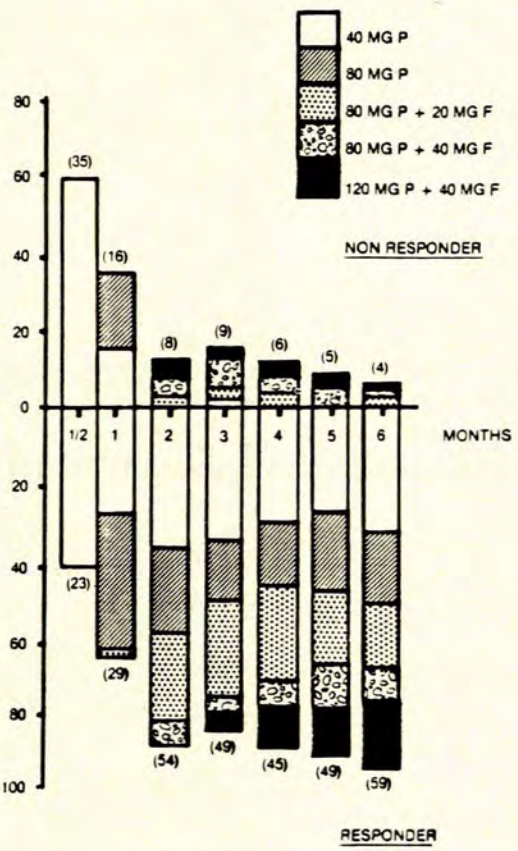

Fig. 4. Percentages of 'responders' and 'non-responders' at each visit (supine diastolic blood pressure).

systolic and diastolic pressure (note: the class interval for systolic pressure is 20 mmHg and that for diastolic pressure 10 mmHg) at 2 weeks is attributable to 40 mg of penbutolol alone. What is more impressive in practical terms is the consistent leftward trend apparent at 6 months. While this result has been produced by combined therapy, these figures represent the high yield in terms of responsiveness to be expected from a simple step-wise combined therapy approach such as used here.

A further global assessment of efficacy of the different treatment regimens was obtained by differentiating 'responders' and 'non-responders'. Defined as 'responders' were those patients showing a reduction in blood pressure of $> 10\%$ of the baseline value (final placebo visit) *and/or* those who achieved a blood pressure of $< 155/95$ mmHg. These results (Figs 3 and 4) show that about 60% (systolic pressure), or 40% (diastolic pressure) of patients exhibited a good response to treatment with penbutolol 40 mg alone. When the penbutolol dose was doubled and again when furosemide 20 mg was added to 80 mg penbutolol, an additional gain in the responder frequency was observed. Only very few patients benefited from a further increase of penbutolol to 120 mg daily or a higher concomitant dose of furosemide.

Heart rate

The frequency histograms for the supine heart rate are shown in Fig. 5. As expected, there was a significant reduction in heart rate at 2 weeks after the start of therapy but little change thereafter. When changes in blood pressure were plotted against

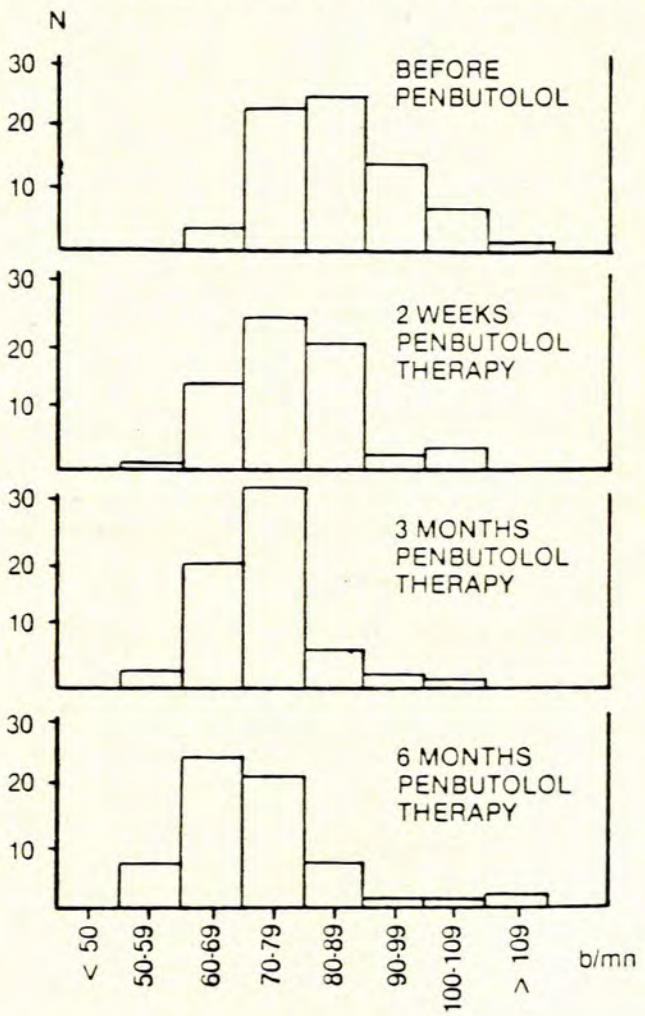

Fig. 5. Frequency distribution of the heart rate (supine) before and during treatment with penbutolol.

changes in heart rate, no significant correlations emerged (correlation coefficient for change in systolic pressure *v.* alteration in heart rate $r = 0,29$; corresponding figure for diastolic pressure $r = 0,06$).

Adverse effects

A number of symptoms which are known to be associated with treatment with ß-blockers occurred during the course of the study. One patient developed signs of congestive cardiac failure, 3 others complained of mild shortness of breath (but not sufficient for them to stop treatment) and 1 developed paraesthesiae in her fingers which persisted for some 3 months but subsequently resolved, although treatment with penbutolol (plus furosemide) was continued.

A number of patients complained of vague symptoms of dizziness, weakness, drowsiness and unsteadiness, but in none was this sufficiently severe for them to discontinue treatment. The only apparent adverse effects not related to ß-blockade were gastro-intestinal complaints (in 8 patients) — notably nausea and abdominal cramps.

In several cases this was clearly an initiation effect and the symptoms disappeared as treatment was continued; in others the symptoms resolved when the medication was taken with food. There was no relationship with the dose.

Schirmer test

Most patients had a Schirmer test to measure tear production at the beginning of the study and at the end of the 6-month period. Two patients in whom the pre-test was normal showed evidence of hyposecretion at the end of the study. Neither of these patients was symptomatic and both continued on treatment. Three other patients had abnormal tests at the end of the study but none of these had had a pre-test. In 2 of these patients the test subsequently became normal, in one after a further 4 months (10th month) and in the other after a further 6 months (12th month) of treatment with penbutolol. It was not necessary

TABLE III. MEDIAN (25 - 75% QUANTILES) OF HAEMATOLOGICAL AND BIOCHEMICAL FINDINGS IN PATIENTS BEFORE AND AFTER 3 - 6 MONTHS' TREATMENT WITH PENBUTOLOL ALONE OR IN COMBINATION WITH FUROSEMIDE

	No.	Before treatment	After 3-6 months' treatment
Haemoglobin (g/dl)	**66**	**14,5 (13,5 - 15,6)**	**14,3 (13,5 - 14,9)**
Haematocrit (%)	**66**	**43 (40 - 46)**	**43 (40 - 45)**
RBC (x10^6/µl)	**56**	**4,6 (4,4 - 5,0)**	**4,7 (4,6 - 4,9)**
WBC (x10^3/µl)	**67**	**6,7 (5,5 - 8,2)**	**6,4 (5,5 - 7,7)**
Neutrophils (%)	**64**	**64 (58 - 70,5)**	**60 (56 - 66)**
Lymphocytes (%)	**64**	**32 (27,5 - 37)**	**34 (29,5 - 39,5)**
Thrombocytes (%)	**61**	**250 (218 - 320)**	**279 (225 - 313)**
Glucose (mg/dl)	**60**	**85 (76,5 - 94,5)**	**84,5 (76 - 96)**
Urea (mg/dl)	**52**	**30,5 (25,5 - 37,5)**	**34,0 (28,0 - 40,0)**
Creatinine (mg/dl)	**67**	**0,9 (0,8 - 1,1)**	**0,9 (0,8 - 1,0)**
Uric acid (mg/dl)	**65**	**6,2 (5,2 - 6,9)**	**6,2 (5,2 - 6,8)**
Sodium (nmol/l)	**67**	**140 (138 - 143)**	**140 (138 - 142)**
Potassium (nmol/l)	**67**	**4,3 (4 - 4,8)**	**4,4 (4 - 4,7)**
Chloride (nmol/l)	**66**	**104 (101 - 106)**	**104,5 (102 - 107)**
Triglyceride (mg/dl)	**66**	**146,5 (110 - 184)**	**149 (123 - 190)**
Protein (g/dl)	**61**	**7,2 (7,0 - 7,6)**	**7,2 (6,8 - 7,4)**
Cholesterol (mg/dl)	**67**	**255 (232 - 300)**	**264 (230 - 294)**
SGOT (mU/nl)	**61**	**14 (10 - 20)**	**13 (10 - 16)**
SGPT (mU/nl)	**61**	**17 (11 - 22)**	**14 (12 - 19)**
Alkaline phosphatase (mU/nl)	**49**	**111 (76 - 140)**	**112 (81 - 131)**

to discontinue treatment in any patient and there were no complaints attributable to the study drug.

Haematological and biochemical findings

Table III gives the median (25-75% quantiles) of the laboratory measurements before and at the end of the 3 - 6-month period. No clinically relevant changes in any of the haematological values were observed. One patient with chronic glomerulonephritis demonstrated a marked deterioration in renal function during the 6-month treatment period (pretreatment levels: urea 49 mg/dl, creatinine 2,0 mg/dl; post-treatment levels: urea 96 mg/dl, creatinine 3,2 mg/dl). Marked proteinuria persisted throughout the trial in spite of a reduction in blood pressure so it seems likely that this rise in urea reflected progress of the underlying disease. Otherwise there were no changes in the biochemical values of any clinical significance. Similarly, urinalysis revealed no relevant abnormalities attributable to the treatment.

Discussion

The results of this study confirm other published reports of the efficacy of penbutolol in moderate hypertension when administered as a single daily dose. No long-term trials have been published previously. Our results show that 60 - 70% of an unselected group of patients with moderate essential or renal hypertension will respond adequately to treatment with penbutolol alone. In these patients the most marked reduction in blood pressure was seen within the first 2 weeks of treatment and this effect was then maintained for the several months of the study.

Some patients experienced gastro-intestinal side-effects at the beginning of treatment. These were not severe and subsequently resolved while the drug was continued. Similar side-effects have been noted in a previous study with penbutolol[12] and may be avoided by administering penbutolol with food.

The addition of furosemide in the more severely hypertensive patients who showed a poor response to penbutolol alone produced an additional hypotensive effect. No adverse reactions to the combination were seen. The combined use of penbutolol and furosemide has been studied previously in a double-blind controlled study and was shown to result in lower doses of each component for a similar or better antihypertensive effect. (Vander Elst *et al.* — Hoechst internal report). Furosemide has also been shown to be as effective as hydrochlorothiazide in enhancing the hypotensive effects of propranolol.[14] Penbutolol therefore appears to be effective and well tolerated in the long-term treatment of hypertension. Its combination with small doses of furosemide in the more serious cases results in a clinically relevant additional antihypertensive effect with excellent tolerance.

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